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| 09/728,309 | 11/30/2000 | Jian Zhang | 18136-1050 | 8694 |

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| EXAMINER |
|---|
| BRANNOCK, MICHAEL T |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1646 | |

DATE MAILED: 06/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

| Application No. | Applicant(s) |
|---|---|
| 09/728,309 | Zhang et al. |
| **Examiner** | **Art Unit** |
| Michael Brannock | 1646 |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1) ☒ Responsive to communication(s) filed on *Apr 1, 2003* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

**Disposition of Claims**

4) ☒ Claim(s) *1-42* is/are pending in the application.

4a) Of the above, claim(s) *9, 16-24, and 28-42* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-8, 10-15, and 25-27* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

**Application Papers**

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *13, 14*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

### *Status of Application: Claims and Amendments*

1. Applicant is notified that the amendments presented as Paper 15, 4/1/03, have been entered in full.

2. Claims 1-42 are pending.

3. Claims 9, 16-24 and 28-42 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, as set forth previously.

4. Applicant is notified that any outstanding objection or rejection that is not expressly maintained in this Office action has been withdrawn in view of Applicant's amendments.

### *Claim Rejections - 35 USC § 101*

5. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

6. Claims 1-8, 10-15, 25-27 stand rejected under 35 U.S.C. § 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility, as set forth previously and reiterated below. The claims are directed to polynucleotides encoding polypeptides of SEQ ID NO: 3, and truncated versions thereof e.g. SEQ ID NO: 4 and 6. The instant specification puts forth that the polypeptide is a human

pheromone receptor (e.g. page 13), although the specification does not assert that the polypeptide binds any particular pheromone or any particular ligand. The specification asserts that the polypeptide is useful in a screening method to determine what ligands may activate or inhibit the polypeptide and also to determine what the physiological effects of the polypeptide might be (see page 13 example). This proposed use lacks a specific and substantial utility. It is not a specific use because any integral membrane protein could be used in exactly the same way. Further, many polypeptides are known in the art, yet the polypeptides have no known function or known ligands. Any of these orphan clones could be used in the manner described in the specification for the claimed polypeptide.

Furthermore, the proposed use of the polypeptide to screen for ligands of the polypeptide or for biologic effects of the polypeptide is not a substantial utility. A substantial utility is a practical use which amounts to more than a starting point for further research and investigation and does not require or constitute carrying out further research to identify or reasonably confirm what the practical use might ultimately be. For example, an assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would be a practical use of the material. However, a method of treating an unspecified disease or condition with a material that has no particular correlation with a disease would not constitute a substantial utility. Basic research, such as studying the properties of the claimed product or the mechanisms in which the product is involved, does not constitute a substantial utility.

The specification puts forth that the polypeptide could be involved in any number of disparate disease states, and could therefore be used as a diagnostic or therapeutic agent (see page 13, for example). A stated belief that a correlation exists between the polynucleotides or polypeptides and any number of diseases is not sufficient guidance to use the claimed polynucleotides to treat and/or diagnosis a particular disease; it merely defines a starting point for further research and investigation.

The instant application has failed to provide guidance as to how one of skill in the art could use the claimed invention in a way that constitutes a specific or substantial utility. The proposed uses of the claimed invention are simply starting points for further research and investigation into potential practical uses of the claimed nucleic acids.

Applicant argues that the connection between vomeropherins, receptors in the human VNO, and the physiological/psychological effect of the vomeropherins is well established and, also, that receptor based assays to identify prospective drug candidates are well understood as part of the drug discovery process. This argument has been fully considered but not deemed persuasive. The instant specification makes no connection between the instant protein and any physiologic effect, or any ligand. The specification has merely invited the artisan to try to discover such effects or ligands. Such and invitation to preform research on the claimed product is not a patentable utility.

7. Claims 1-8, 10-15, 25-27 are also rejected under 35 U.S.C. § 112 first paragraph, as set forth previously and reiterated below. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art would not know how to use the claimed invention so that it would operate as intended without undue experimentation.

Furthermore, the claims encompass polynucleotides which merely hybridize to the polynucleotides encoding SEQ ID NO: 3. Thus the claims encompass a vast genus of polynucleotides encoding polypeptide variants of the polypeptide of SEQ ID NO: 3, i.e. substitutions, deletions or insertions in a protein corresponding to SEQ ID NO: 3; should Applicant establish a specific and substantial utility for the claimed polynucleotides, Applicant has not provided sufficient guidance as to how to make and use the encoded polypeptides which are not 100% identical to the polypeptide of SEQ ID NO: 3, but which still retain a desired property of the polypeptide of SEQ ID NO: 3. The claims require polynucleotides comprising only portions which hybridize to a polynucleotide encoding SEQ ID NO: 3, e.g those that hybridize to a polynucleotide encoding a fragment of SEQ ID NO: 3. Thus, the vast majority of encoded polypeptides are amino acid sequence variants of SEQ ID NO: 3, i.e. amino acid substitutions, deletions or insertions in a protein corresponding to SEQ ID NO: 3, yet the specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make. Furthermore, Applicant has not provided guidance as to what properties of the allelic variants or sequence variants of the protein corresponding to SEQ ID NO: 3 might be

desired nor any guidance as to which amino acid substitutions, deletions or insertions to make to achieve any desired property. Applicant has not defined a difference in structure or difference in function between the protein corresponding to SEQ ID NO: 3 and variants of said protein. If a variant of the protein corresponding to SEQ ID NO: 3 is to have a structure and function similar to the protein corresponding to SEQ ID NO: 3, then the specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make that will preserve the structure and function of the protein corresponding to SEQ ID NO: 3. Conversely, if a polynucleotide encoding a protein variant of SEQ ID NO: 3 need not have a disclosed property, the specification has failed to teach how to use such a polynucleotide.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al., 1990, Science 247:1306-1310, especially p.1306, column 2, paragraph 2). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art

to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Also, these or other regions may be critical determinants of antigenicity. It is well appreciated in the art of antibody production that it is unpredictable which amino acids are critical antigenic determinants (see Alexander et al., Proc. Natl. Acad. Sci. 89(3352-3356)1992. Protein antigenicity can be significantly reduced by substitution of even a single residue. Further, even if an amino acid substitution does not destroy the activity of the immunizing protein, the substitution may significantly reduce the antigenicity of the protein (see the Abstract of Alexander et al.). The specification does not provide sufficient guidance as to how to make antibodies that are specific to variants of SEQ ID NO: 3 that can be used for any specific purpose. Although the specification suggests that polynucleotides that hybridize to the disclosed polynucleotides, under high, medium, or low stringency, can be used to find other "related" polynucleotides the specification has not indicated what exactly these other related polynucleotides can be used for - other than as a starting point for further research and investigation into the particular properties of the polynucleotides.

The specification has failed to provide an activity of SEQ ID NO: 3 to be used to evaluate the claimed variants for usefulness. The specification has not provided a working example of the use of the polypeptide of SEQ ID NO: 3 or a variant of the polypeptide of SEQ ID NO: 3 nor sufficient guidance so as to enable one of skill in the art to make such a variant with any particular use. The specification has failed to teach which amino acids of SEQ ID NO: 3 could be

modified so as to produce a polypeptide that is not identical to SEQ ID NO: 3 and yet still retain the activity of the polypeptide of SEQ ID NO: 3 - which has apparently not been disclosed. The specification has not provided sufficient instruction as to how to find the activity of any such pheromone receptor polypeptide. The specification has provided no working example of a functional cloned pheromone receptor (from any species) and nor does such appear to be recognized in the art. Commenting on the state of the art, Dulac et al.,Current Opinion in Neurobiology 10(511-118)2000, indicate that even in the field of rodent pheromone receptor biology, there exists a lack of functional studies able to match a pheromone ligand with a putative pheromone receptor, see page 512, col 2. The instant specification does not appear to address this art-recognized problem, yet the claims require methods of producing a pheromone receptor, i.e. a protein capable of recognizing a pheromone. The art does not appear to recognize the heterologous expression of a pheromone receptor in any host cell. Claims 6-15 require vectors and host cells capable of expressing a pheromone receptor. The specification provides no working example of such vectors and host cells, and merely asserts that such can be accomplished.

Thus, due to the large quantity of experimentation necessary to generate the infinite number of variants recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the

effects of mutation on protein structure and function, the lack of direction provided in the specification as to how to use the encompassed variants, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Applicant argues that the claimed genus is not overly broad and that the artisan could make such without undue experimentation. This argument has been fully considered but not deemed persuasive for the reasons specifically stated above.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1, 2, 3-15 and 25-27 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses a polynucleotide of SEQ ID NO: 1 and two variants, yet the claims encompass a vast genus of polynucleotides not described in the specification, i.e. polynucleotides which comprise only portions of SEQ ID NO: 1, e.g. sequences from other species, mutated sequences, allelic variants, or sequences that can be used to identify related

pheromone receptors. None of these sequences meet the written description provision of 35 U.S.C. 112, first paragraph. Although one of skill in the art would reasonably predict that these sequences exist, one would not be able make useful predictions as to the nucleotide positions or identities of those sequences based on the information disclosed in the specification.

The instant disclosure of a single polynucleotide, that of SEQ ID NO: 1 and two variants, encoding a polypeptide with no instantly disclosed specific activities, does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera. A genus claim may be supported by a representative number of species as set forth in *Regents of the University of California v Eli Lilly & Co,* 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. The instant specification discloses, however, a single isolated polynucleotide sequence SEQ ID NO: 1 and two single nucleotide variants, which are not sufficient to describe the essentially limitless genera encompassed by the claims.

The instant claims are not directed to that which is disclosed as essential to the invention, i.e. something that is homologous to the parent SEQ ID NO: 1 and has the function of the parent polynucleotide. Thus, with the exception of the of the polynucleotides disclosed, and other polynucleotides which encode a polypeptide of SEQ ID NO: 3, the skilled artisan cannot envision encompassed variants. Therefore, only polynucleotides encoding a polypeptide of SEQ

ID NO: 3, and polynucleotides *consisting* of fragments thereof, or polynucleotides consisting of fragments thereof and heterologous sequences (e.g. carrier or tag sequences), but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112, first paragraph.

Further, Claims 6-15 require vectors and host cells capable of expressing a pheromone receptor. The art does not appear to recognize the heterologous expression of a pheromone receptor in any host cell (see above). The specification provides no working example of such vectors and host cells, and merely asserts that such can be accomplished. Thus, the skilled artisan, with knowledge of the field of pheromone receptor biology, would not recognize that Applicant was in possession of such vectors and host cells.

Applicant argues that the claims have been amended to require that the sequences either hybridize to the described polynucleotide or encode the described protein. This argument has been fully considered but not deemed persuasive, however it is noted that claim 3 has been removed from the rejection because of the amendment. Further, it is noted that the specification provides an adequate written description of nucleic acids encoding a polypeptide of SEQ ID NO: 3, 4 and 6, yet no claim is so limited. Regarding Applicant's assertion that hybridization conditions provide an adequate written description of the hybridizing nucleic acids, the property of hybridization does not describe the sequence identity of any one of the essentially limitless number polynucleotides encompassed by the claims. Hybridization is simply a general property resulting from the cumulative effect of multiple interactions between two nucleic acids, and does

not, alone, provide a description of the nucleic acids, such that the artisan would recognized that Applicant was in possession of such a limitless genus as that which is claimed.

***Conclusion***

No claims are allowable.

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (703) 306-5876. The examiner can normally be reached on Mondays through Thursdays from 8:00 a.m. to 5:30 p.m. The examiner can also normally be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

GARY KUNZ
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

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June 15, 2003